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Research report

Ventromedial prefrontal cortex damage alters resting blood flow to the bed nucleus of stria terminalis

Julian C. Motzkin [a,b,c], Carissa L. Philippi [a], Jonathan A. Oler [a], Ned H. Kalin [a], Mustafa K. Baskaya [d] and Michael Koenigs [a,*]

[a] Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, USA
[b] Neuroscience Training Program, University of Wisconsin-Madison, Madison, WI, USA
[c] Medical Scientist Training Program, University of Wisconsin-Madison, Madison, WI, USA
[d] Department of Neurological Surgery, University of Wisconsin-Madison, Madison, WI, USA

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ABSTRACT

The ventromedial prefrontal cortex (vmPFC) plays a key role in modulating emotional responses, yet the precise neural mechanisms underlying this function remain unclear. vmPFC interacts with a number of subcortical structures involved in affective processing, including the amygdala, hypothalamus, periaqueductal gray, ventral striatum, and bed nucleus of stria terminalis (BNST). While a previous study of non-human primates shows that vmPFC lesions reduce BNST activity and anxious behavior, no such causal evidence exists in humans. In this study, we used a novel application of magnetic resonance imaging (MRI) in neurosurgical patients with focal, bilateral vmPFC damage to determine whether vmPFC is indeed critical for modulating BNST function in humans. Relative to neurologically healthy subjects, who exhibited robust rest-state functional connectivity between vmPFC and BNST, the vmPFC lesion patients had significantly lower resting-state perfusion of the right BNST. No such perfusion differences were observed for the amygdala, striatum, hypothalamus, or periaqueductal gray. This study thus provides unique data on the relationship between vmPFC and BNST, suggesting that vmPFC serves to promote BNST activity in humans. This finding is relevant for neural circuitry models of mood and anxiety disorders.

1. Introduction

The ventromedial prefrontal cortex (vmPFC) plays a critical role in human social and affective processing. Dysfunction in this brain area is thought to be a key neural substrate underlying the pathophysiology of mood and anxiety disorders (Critchley, Mathias, & Dolan, 2001; Drevets, Price, & Furey, 2008; Milad, Rauch, Pitman, & Quirk, 2006; Myers-Schulz &

* *Corresponding author*. Department of Psychiatry, University of Wisconsin-Madison, 6001 Research Park Blvd., Madison, WI, 53719, USA.
E-mail address: mrkoenigs@wisc.edu (M. Koenigs).
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Koenigs, 2012; Price, 1999). However, the precise mechanisms by which vmPFC dysfunction contributes to affective psychopathology are not fully understood. A leading neural circuit model proposes that vmPFC serves to regulate negative affect via top-down inhibition of brain regions involved in processing negative emotion—particularly the amygdala—and that pathologically elevated levels of negative affect in mood and anxiety disorders result from deficient vmPFC-mediated inhibition of amygdala activity (Milad et al., 2006; Quirk & Gehlert, 2003; Rauch, Shin, & Phelps, 2006). While this model is consistent with a considerable body of anatomical, behavioral, and neurophysiological data from rodent fear conditioning paradigms (Milad et al., 2006), studies of human lesion patients suggest a more complex role of vmPFC in affective function. For instance, although vmPFC lesion patients exhibit increased amygdala activity in response to aversive stimuli (Motzkin et al., 2015), vmPFC damage has been shown to *reduce* the likelihood of developing PTSD and depression (Koenigs, Huey, Calamia, et al., 2008; Koenigs, Huey, Raymont, et al., 2008). These findings suggest that vmPFC may coordinate multiple neural processes critical for the expression of negative affect in humans. Beyond top-down inhibition of amygdala, vmPFC may also modulate activity in other regions, such as the bed nucleus of the stria terminalis (BNST).

The BNST is a basal forebrain structure that is considered to be a component of the "extended amygdala" complex, in light of similarities in development, connectivity, and cytoarchitecture to the adjacent central nucleus of the amygdala (Heimer, Harlan, Alheid, Garcia, & de Olmos, 1997). The BNST and vmPFC are strongly interconnected (Avery et al., 2014), and BNST activity has been linked to anxiety-related behavior (Davis & Whalen, 2001; Kalin, Shelton, Fox, Oakes, & Davidson, 2005; Mobbs et al., 2010; Somerville, Wagner, et al., 2013; Somerville, Whalen, & Kelley, 2010; Straube, Mentzel, & Miltner, 2007; Walker, Toufexis, & Davis, 2003). Moreover, a previous neuroimaging study in non-human primates found that bilateral orbitofrontal cortex (OFC) lesions (which included regions of vmPFC) were associated with reduced BNST metabolism and reduced anxious behavior in a human intruder paradigm (Fox et al., 2010; Kalin, Shelton, & Davidson, 2007). In addition, across the lesioned and non-lesioned monkeys, the level of BNST metabolism positively correlated with the degree of anxious behavior. These findings suggest that vmPFC/OFC may play a crucial role in generating or maintaining negative affect by promoting BNST activity. To explore this hypothesis in humans, we employed a magnetic resonance imaging (MRI) measure of resting cerebral blood flow (CBF) in a sample of neurosurgical patients with circumscribed bilateral vmPFC lesions. We hypothesized that, consistent with the results of the non-human primate study (Fox et al., 2010), humans with bilateral vmPFC damage would exhibit reduced BNST blood perfusion, which would in turn correlate with self-report measures of negative affect and anxiety. Furthermore, we used rest-state fMRI in the healthy adult comparison group to assess functional connectivity between BNST and vmPFC.

2. Methods

2.1. *Participants*

The lesion group consisted of four adult neurosurgical patients with extensive bilateral parenchymal damage, largely confined to the vmPFC—defined as the medial one-third of the orbital surface and the ventral one-third of the medial surface of prefrontal cortex, bilaterally (Fig. 1). Each of the four

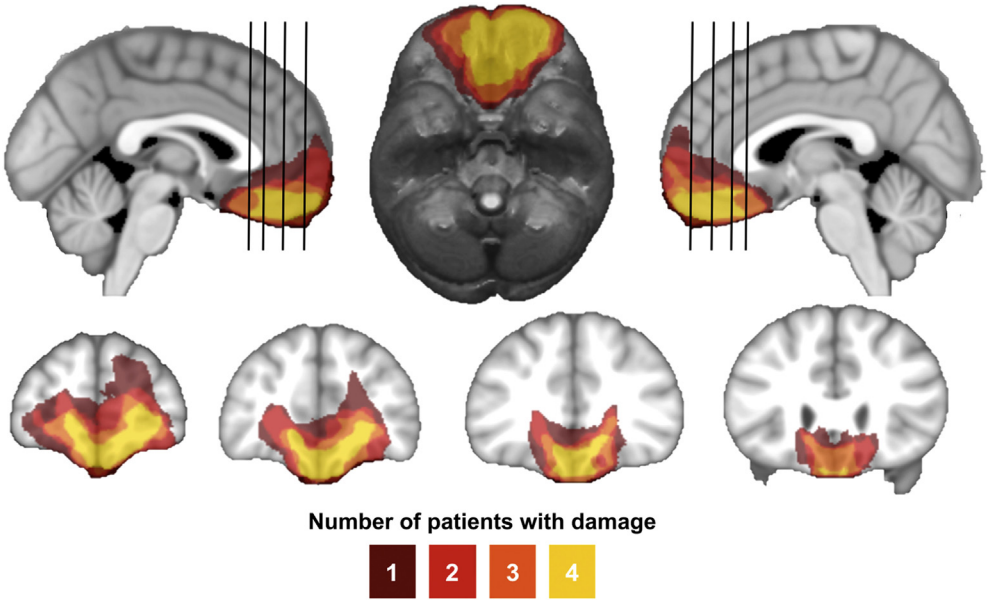

Fig. 1 – Lesion overlap of vmPFC patients. Color indicates the number of overlapping lesions at each voxel. All vmPFC patients had damage to the medial one-third of the OFC and the ventral one-third of medial surface of prefrontal cortex, bilaterally. This area includes Brodmann areas 11, 12, 24, 25, 32, and the medial portion of 10 below the level of the genu of the corpus callosum, as well as subjacent white matter.